Reactivity Studies of Donor-Acceptor Cyclopropanes: Is there a Relation to Structural and Electronic Properties?

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Dedicated to Professor Armin de Meijere on the occasion of his 80th birthday

Abstract: *The kinetics of 18 different donor-acceptor cyclopropanes in the (3+2)-cycloaddition reaction with aldehyde were studied by in-situ NMR spectroscopy. Increasing the electron density of the donor residue accelerates the reaction to a factor up to 50 compared to the unsubstituted one whereas electron withdrawing substituents slow down the reaction 660 times. This behavior is in agreement with the Hammett substituent parameter σ. The obtained rate constants form the (3+2)-cycloaddition correlated well with respective data from additionally studied (3+n)-cycloadditions with nitrone (n = 3) and isobenzofurane (n = 4). A comparison of the kinetic data with bond lengths in the cyclopropane (obtained by X-ray and computations), and ^{1}H and ^{13}C NMR shifts revealed no correlation. However, computed relaxed force constants of D-A cyclopropanes proved to be a good indicator for the reactivity of the three-membered-ring.*

Cyclopropane, the smallest and most strained cycloalkane is a kinetically rather inert molecule. However, if donor and acceptor moieties are installed at adjacent positions its reactivity is tremendously increased. In the late 70s and 80s of last century, Wenkert and Reissig have developed the first ground-breaking reactions using donor-acceptor (D-A) cyclopropanes.[1] Key to understand the reactivity of the three-carbon entity is the weak, highly polarized bond between donor and acceptor which might be regarded in its extreme as a 1,3-zwitterion.[2]

After a time of hibernation, for the last decade, D-A cyclopropanes have enjoyed an intense renaissance. Numerous novel rearrangements,[3] cycloadditions,[4, 5] ring-opening reactions[6] and even enantioselective transformations[7] exploiting both, the ring strain and the polarized bond, were designed. Previously uninvestigated donors and acceptors came into the focus,[8] and their special reactivity was used as key step in total syntheses of natural products.[9] Although the field has been rapidly evolving, there is still a great lack on physical-organic data regarding reactions of donor-acceptor cyclopropanes. To the best of our knowledge, there is neither a comparative analysis of kinetic data in this field nor a comparative structural analysis of ground-state geometrical parameters using a series of closely related D-A cyclopropanes differing in their substitution pattern.

With this paper, we would like to close this gap. We demonstrate that kinetic rate constants range over more than four orders of magnitude. These results are compared with structural data obtained by X-ray analyses or DFT calculations. Furthermore, we computed relaxed force constants within this series which are a good indicator for the weakness of a bond based on ground state properties.

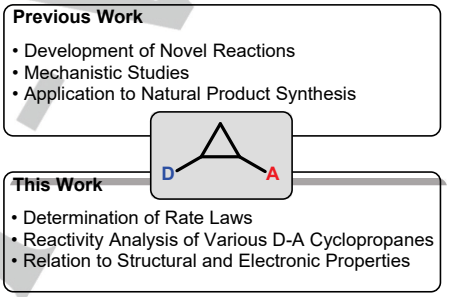

Figure 1. Closing the gap: Determination of kinetic and structural data.

For our study we used the most commonly employed type of donor-acceptor cyclopropane that bears two geminal carboxylic ester moieties and aryl or heteroatom substituents in adjacent position. To start our kinetic investigations of different donor-acceptor systems **1** we chose a simple (3+2)-cycloaddition reaction inserting aldehyde **2** into the three-membered ring system (Table 1). The advantage of this reaction is that tin(IV) chloride is able to act as a catalyst. In contrast to many other Lewis acids that are commonly employed in D-A cyclopropane chemistry it is soluble in dichloromethane, thus, allowing an exact determination of its concentration. First, we deduced the rate law of the reaction and found a first order kinetic with regard to the aldehyde. Because of a minor concentration of the activating Lewis acid, we found a zero-order dependence for the cyclopropane for high concentration of this substrate. Consequently, we specified a pseudo first-order kinetic for our system (rate law: $d[product]/dt = -k\cdot[cyclopropane]^{0}\cdot[aldehyde]^{1}$). For all these experiments we relied on ^{19}F NMR spectroscopy since the reacting 4-fluorobenzaldehyde and the emerging five-membered THF derivative **3** show characteristic ^{19}F chemical shifts.[10] As internal standard α,α,α-trifluorotoluene was added. The rate constants of 18 different D-A cyclopropanes were determined by monitoring the decrease of the concentration of 4-fluorobenzaldehyde (Table 1, Fig. a)) and subsequent logarithmic evaluation of the measured data by least square fitting (Table 1, Fig. b). The determined constants from the slope of the fitting function were taken relative to the value of the D-A cyclopropane with phenyl as donor. Mechanistic studies by

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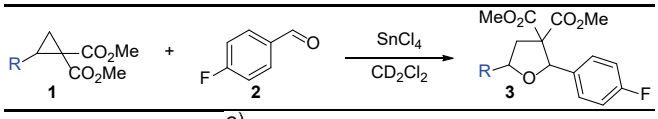
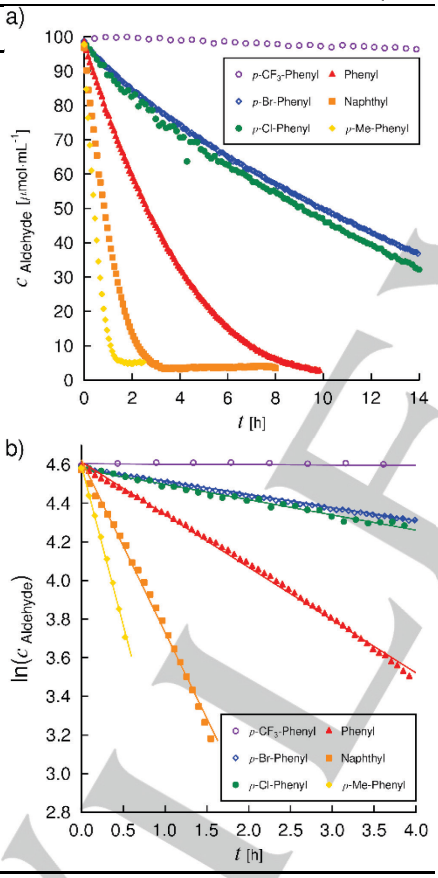
Johnson and coworkers revealed an unusual substitution process with a close ion-pair as electrophile.[11] With this mechanism in hand, it was expected and confirmed that electron-rich donors on the cyclopropane led to very fast reaction times (e.g. *p*-methoxyphenylcyclopropane k_{rel} = 49.7, entry a). In addition, an enlargement of the π-system by taking a naphthyl residue (entry e) as donor led to an acceleration of the reaction by a factor of three. Halogen-substituted donors slowed the reaction only slightly (entries h, k, and l) while a decrease of the π-system achieved by introducing a double bond as donor (entry n) led to a slowdown to about 1%. Very electron-poor donors such as *p*-F_3C-phenyl (entry p) or *p*-O_2N-phenyl (entry r) led to radically decelerated reactions.

Table 1. Measurement of the relative reaction rate constants of the reaction of 4-fluorobenzaldehyde with different D-A cyclopropanes.[12]



	Residue	k_{rel}[a]
a	*p*-MeO-Ph[b]	49.7
b	Phthalimide	42.0
c	*p*-Me-Ph	6.32
d	*o*-MeO-Ph	3.20
e	Naphthyl	3.12
f	Cyclopropyl	1.92
g	**Ph**	**1.00**
h	*p*-F-Ph	0.62
i	*o*-Me-Ph	0.50
j	Ph[c]	0.32
k	*p*-Cl-Ph	0.27
l	*p*-Br-Ph	0.25
m	Ph[d]	0.22
n	Succinimide	0.12
o	H_2C=CH-	0.093
p	*p*-F_3C-Ph	0.0077
q	*m*-O_2N-Ph	0.0017
r	*p*-O_2N-Ph	0.0015



Reaction conditions: D-A cyclopropane (1.00 equiv.), 4-fluorobenzaldehyde (1.00 equiv.), $SnCl_4$ (0.10 M in CH_2Cl_2, 0.015 equiv.), CD_2Cl_2 (0.10 M), 298 K. [a] $k_{rel} = k_{Residue} / k_{Phenyl}$. [b] The fast formation of a side product was observed. [c] Benzyl ester instead of methyl ester. [d] Ethyl ester instead of methyl ester.

It should be noted that even the classical Waser cyclopropanes, i.e. cyclopropanes with nitrogen atoms as donors, differ strongly in their kinetic behavior. The phthalimide donor (k_{rel} = 42.0, entry b) is about 350 times faster than the succinimide donor (k_{rel} = 0.12, entry n). Furthermore, the influence of different esters as acceptors on the reaction was investigated. Both changes to ethyl esters (entry m) or benzyl esters (entry j) caused a slowdown in the speed of the reaction, probably because of a sterically more difficult coordination being traced back to the bulkier groups. Overall, the reaction time vary by four orders of magnitude. While the phenyl cyclopropane showed full conversion after about ten hours, this time accelerated to a few minutes in the case of the *p*-methoxyphenylcyclopropane. The use of cyclopropanes with strongly electron-withdrawing groups showed hardly any turnover even after four days. With such long reaction times, the conditions need of course be adjusted for "real" transformations, since the reliability of the reagents in solution cannot be guaranteed after several days.

A plot of the measured logarithmic rate constants for *p*-substituted D-A cyclopropanes against tabulated Hammett substituent parameters[13] revealed an excellent correlation of this data (Figure 2). The negative slope (i.e. the reaction parameter ρ) of the regression line showed that a more electron-rich donor influences the rate-determining step resulting in a faster reaction.

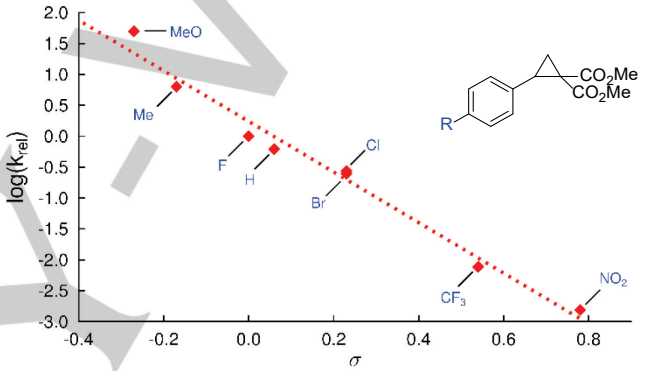


Figure 2. Hammett plot.

For a systematic discussion of the particular influences of different substituents attached at the donor moiety, we compared the acquired kinetic data of *p*-substituted phenyl cyclopropanes to different physical parameters (Table 2). To our surprise, neither the calculated bond lengths in gas phase nor the measured bond lengths in solid state showed a tendency suitable to the shown kinetic trend although we expected a longer bond length (i.e. weaker bond) for a better donor (in total, crystal structure data of nine different D-A cyclopropanes were evaluated, see SI for further information).[14] The NMR shifts (^{1}H and ^{13}C) of the carbon and hydrogen next to the donor also showed no correlation of any kind to the rate constants.

Table 2. Comparison of physical parameters for *p*-substituted D-A cyclopropanes.

Donor	Bond length gas phase[a] [Å]	NMR shift C-2-**H** [ppm]	NMR shift **C**-2 [ppm]	RFC[b] [mdyn/ Å]
p-MeO-Ph	1.561	3.17[15]	32.1[15]	2.584
p-Me-Ph	1.559	3.19[15]	32.4[15]	2.646
Naphthyl	1.559	3.38[16]	32.9[16]	2.660
Ph	1.558 (1.539)	3.22[15]	32.4[15]	2.688
p-F-Ph	1.558	3.19[17]	31.7[17]	2.674
p-Cl-Ph	1.558 (1.537)	3.16[18]	30.7[18]	2.688
p-Br-Ph	1.558 (1.536)	3.21[18]	32.6[18]	2.688
p-CF_3-Ph	1.556 (1.549)	3.25[19]	29.7[19]	2.725
p-NO_2-Ph	1.556 (1.542)	3.28[17]	31.5[17]	2.732

[a] B3LYP/6-311G(d,p), values in brackets: bond length in solid state from X-ray analysis. [b] RFC = Relaxed force constant.

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Next, we calculated the relaxed force constants (RFC) of the bond broken in the cyclopropane during the reaction.[20] Indeed, these parameters showed a good correlation to the kinetic data (Figure 3).[21] It has been observed that a higher rate constant is associated with a lower RFC, which is equal to a weaker bond.

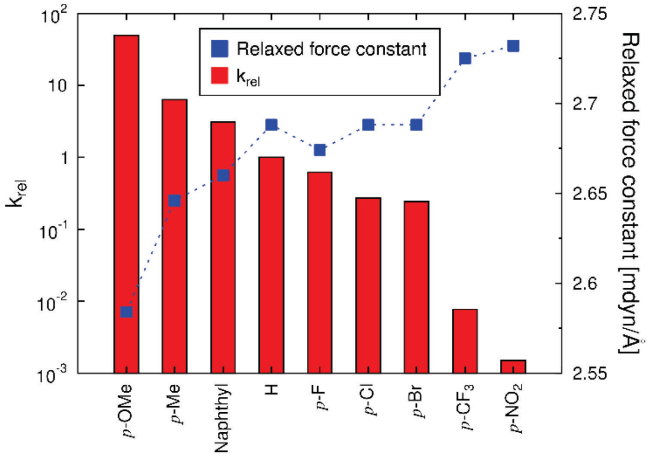

Figure 3. Reaction rate constants (red, logarithmic scale) vs. relaxed force constants of the bond to be broken (blue).

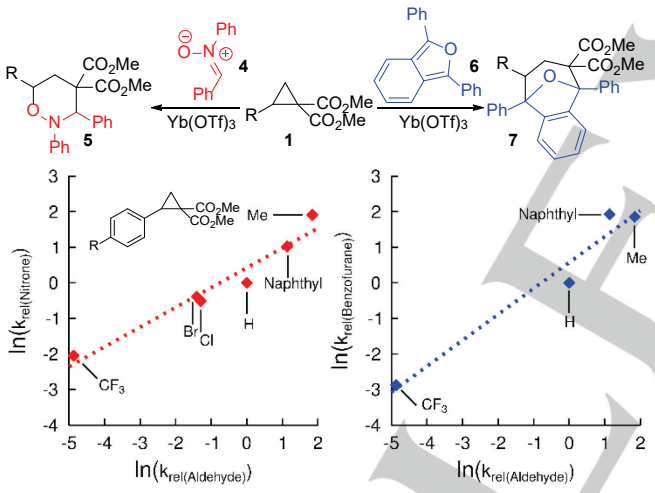

Figure 4. Plotting of the logarithmic specific rate constants of the aldehyde against those of nitrone (red) and isobenzofurane (blue). It was not possible to get reliable data from measuring the halogen-substituted phenyl cyclopropanes in case of the (3+4)-cycloaddition with the isobenzofurane. From a qualitative point of view, however, these measurements also fit into the overall picture.

With these results in hand, we explored whether the kinetic trends observed within the reaction of 4-fluorobenzaldehyde with different D-A cyclopropanes can be reproduced with other cycloaddition reactions. For several D-A cyclopropanes, we investigated both a formal (3+3)- and a (4+3)-cycloaddition by using either nitrone **4** [22] or isobenzofurane **6** [23] as starting materials (Figure 4). The progress of these reactions was analyzed by observing the decrease of characteristic IR bands of the starting materials using *in-operando* IR spectroscopy.[24] An advantage of this method compared to NMR spectroscopy is the considerable shorter time between the recording of two measuring points, the simple use of different solvents and the fast adjustment of parameters such as temperature and stirring of the solution. Furthermore, this technique tolerated the reliable use of solid Lewis acids such as $Yb(OTf)_3$. Logarithmic plotting of the specific rate constants against each other allowed a comparison of the reactions. A linear dependence should result at comparable kinetics. In fact, the reactions with the nitrone showed a good correlation. Overall, the previously observed trend was also reflected in the isobenzofurane reaction (with slight deviations, e.g. naphthyl and p-MePh).

In summary, we demonstrated that D-A cyclopropanes reveal strikingly different kinetic behavior. An electron-releasing substituent on the aryl accelerated the reaction strongly compared to the parent phenylcyclopropane while electron-withdrawing substituents slowed down the reaction heavily. The fastest reaction with a *p*-methoxyphenyl-substituted cyclopropane was more than 30 000 times faster than the slowest reaction with a *p*-nitro-substituted derivative. The obtained data showed a perfect correlation with the well-known Hammett substitution parameters. Furthermore, the rate constants were related with different physical parameters. Only the relaxed forced constants showed a satisfactory dependence to the observed reactivity. Finally, we demonstrated that the obtained data are also of use for other cycloaddition reactions indicating a mechanistic similarity of these transformations. Our results will be of high value for a better estimation of reaction times for future reactions involving D-A cyclopropanes or to adjust catalyst loadings in order to achieve more efficient transformations.

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Keywords: cyclopropane • cycloaddition • reactivity study • catalysis • donor-acceptor compounds

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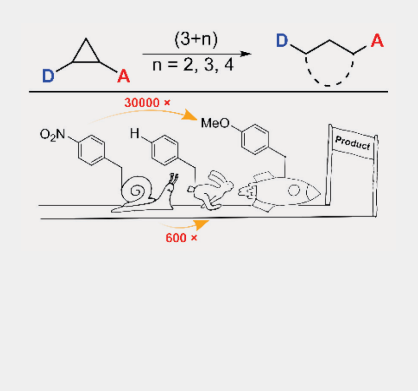
COMMUNICATION

Who is faster? The reactivity of donor-acceptor cyclopropanes was investigated in (3+n)-cycloaddition reactions with aldehyde, nitrone and isobenzofurane by NMR *and in-operando* IR spectroscopy. The obtained reaction rates were compared with structural and electronic properties of donor-acceptor cyclopropanes.



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Page No. – Page No.

Reactivity Studies of Donor-Acceptor Cyclopropanes: Is there a Relation to Structural and Electronic Properties?

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